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CERTIFICATE OF MAILING	
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date appearing below.	
By <u>W B Brader</u>	Date <u>8-19-98</u>
ELI LILLY AND COMPANY	

**PATENT APPLICATION**  
**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants	: Brader, et al.	)	
Serial No.	: 08/484,542	)	
Filed	: 7 June 1995	)	Group Art Unit:
For	: Stabilized Acylated Insulin Formulations	)	1645
Docket No.	: X-10097	)	Examiner:
		)	Allen, M.



**DECLARATION UNDER 37 C.F.R. §1.131**

Assistant Commissioner for Patents

Washington, D. C. 20231

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Sir:

We, Mark L. Brader and Michael J. Beckage, declare that:

We are co-inventors and applicants in this application.

Attached exhibits 1, 2, and 3 are copies of pages from Michael J. Beckage's notebook in which he recorded the preparation of a formulation comprising an aqueous solution of a fatty acid-acylated insulin and approximately 0.35 mole of zinc per mole of said fatty acid-acylated insulin, and having a pH of approximately 7.5. The fatty-acid acylated insulin was N<sup>ε</sup>-Lys<sup>B29</sup>-palmitoyl-human insulin, which is referred to as C16-insulin. The formulation also contained *m*-cresol, a phenolic compound, at a concentration of approximately 2.5 mg/mL.

The dates have been redacted. All the actions, events, and observations described in exhibits 1, 2, and 3 occurred in the United States, prior to 17 November, 1994, the date of the filing of the patent application from which U.S. Patent No. 5,693,609 issued.

We further declare that all statements made herein of our own knowledge are true, that all statements made on

information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of the application or any patent issuing thereon.

4/29/98  
Date

4/29/98  
Date

Mark L. Brader  
Mark L. Brader

Michael J. Beckage  
Michael J. Beckage

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## Reformulation of C16 - Insulin

DBF40 - UV potency 92%

Assume 90% for calculations

U100 insulin = 3.5% mg/ml

$$U100 \text{ C16} = \frac{6046}{5808} \times 3.5\% = 1.041 \times 3.5\% = 3.6435 \text{ mg/ml}$$

$$\frac{3.6435}{0.9 \text{ mg Pot/mg solid}} = 4.05 \text{ mg solids/ml}$$

dissolve in 60% final volume = 6.75 mg/ml

236.25 mg in 35 ml = 6.75 mg/ml

Stock diluent

Glycerol want 16 mg/ml 26.67 mg/ml in stock

6.69 gm in 250 ml 0.1N HCl = 26.76 mg/ml

Lot B1187 16.056 mg/ml after dilution

m-cresol density = 1.035 gms/ml

want final conc = 2.5 mg/ml

$$\text{stock conc} = \frac{2.5}{0.6} = 4.167 \text{ mg/ml} \times 35 = 145.8 \text{ mg}$$

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$$\frac{145.8 \text{ mg}}{1.035 \text{ mg/ml}} = \frac{146.86}{146.09} = 141 \lambda \text{ added}$$

B 64022 QA 168E

Material divided in 1/2

15 ml of protein stock to be diluted to 25 ml

Want .35 mole ratio of Zn to Cl6

$$3.6435 \text{ mg/ml Cl6 final conc} \times 25 \text{ ml} = 91 \text{ mg}$$

$$\frac{91}{6046} = .01505 \text{ mMoles}$$

$$\text{Want } .01505 \times .35 = 5.2679 \times 10^{-3} \text{ mMoles}$$

$$\text{ZnO} = 81.38 \text{ mg/mMole}$$

$$5.2679 \times 81.38 = .428 \text{ mg Zn}$$

$$\frac{.428}{25} = .01712 \text{ mg/ml}$$

ZnO Stock  
Y07223

$$\frac{11}{1.4 \text{ ml } 1 \text{ M HCl}} = 7.857 \text{ mg/ml} + 1.4 \text{ ml H}_2\text{O} = 3.93 \text{ mg/ml}$$

$$\frac{.428 \text{ mg ZnO}}{3.93 \text{ mg/ml}} = .1089 \text{ ml} = 109 \lambda \text{ added}$$

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M Perkin



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## Zn containing formulations

ZB	200λ	1N	NaOH	turbid	
	25λ	1N	NaOH	turbid	
pink	25λ	1N	NaOH	turbid	pH 5.1
	100λ	1N	NaOH	clear	pH 7.88

QS to 25 ml divide in two parts

5λ	1N	NaOH	pH 8.05
5λ	.1N	HCl	pH 8.04
10λ	.1N	HCl	pH 8.0

ZA start with second 1/2 pH 7.88

grey	10λ	1N	HCl	pH 7.42	clear
	5λ	.01N	NaOH	pH 7.49	

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Recorded by: *M. Decker*

Date

Verified by: *JMC*

Date